IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	SCHMIDT	Group Art Unit:	1657
Serial No.:	10/655,889	Examiner:	AFREMOVA, V.
Filed:	SEPTEMBER 4, 2003	Conf. No.:	7191
Atty. File No.:	5662-1-PUS-1-1		
For:	USE OF NEUROTOXIN THERAPY FOR TREATMENT OF UROLOGICAL-NEUROLOGICAL DISORDERS ASSOCIATED WITH PROSTATE CANCER		REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

An Office Action was mailed in the above-captioned application on October 18, 2006. Claims 1, 3-11, 13, 15-19, 21 and 22 were pending in the application. Claims 1, 3-11, 13, 15-19, 21 and 22 were rejected. This Request for Reconsideration document is submitted in response to said Office Action.

The Rejection of Claims 1-19 under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1-19 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention. The second paragraph of Section 112 requires that the claims set out and circumscribe a particular area that applicants regard as their invention with a reasonable degree of precision and particularity.

Specifically, the rejection alleges that the claims are drawn to treating prostate cancer due to the recitation of "a patient with prostate cancer" in Claims 1 and 10 but that "alleviating a symptom" is irrelevant to the treatment of prostate cancer because symptom are not causes of diseases.

Applicant submits that Claims 1 and 10 are clear as written. By definition, symptoms result from or are manifestations of diseases or conditions and do not cause them. It is therefore possible to alleviate a symptom of a disease without treating the underlying cause of the disease itself. It should be self-evident that alleviating a symptom of prostate cancer is possible only in a patient that has prostate cancer. Furthermore, the claims do not recite treating prostate cancer or treating a cause of prostate cancer. There is therefore nothing indefinite in the claimed method, which is directed to alleviation of a symptom of prostate cancer in a patient with prostate cancer.

The rejection asserts that the symptoms recited in claims 3, 4, 10, 13, 20, and 21 would not necessarily point to a patient with prostate cancer. The claims are directed to alleviating a symptom of prostate cancer in a patient with prostate cancer, and claims 3, 4, 13, 20, and 21 recite the specific symptoms of urinary incontinence, urinary retention, urge-type dysfunction, unstable bladder, unstable sphincter, recurrent urinary infection, and prostatic enlargement. While the symptoms listed in these claims may or may not be symptoms of other conditions, they <u>are</u> symptoms of prostate cancer, as clearly described in the Background section of the specification, and the claims are directed to the alleviation of these symptoms, not with respect to "other conditions" or patients in general, but in a patient with prostate cancer. In other words, it is a requirement of the claims that the patent has prostate cancer.

The rejection also states that the claimed invention is indefinite for failing to particularly point out and distinctly claim what is intended by "a therapeutic amount of a botulinum toxin." Applicant respectfully points out that the specification, at page 8, lines 15-18, defines a therapeutically effective amount of a neurotoxin as "the dosage sufficient to inhibit neuronal activity for at least one week, more preferably one month, most preferably for approximately 6 to 8 months or longer." The specification also teaches at page 11, lines 17-19 that "[t]herapeutically effective amounts of botulinum toxin can be any amounts or doses that are less than a toxic dose, for example, less than about 3000 IU/70 kg male, preferably between 100 IU/70 kg male to 1200 IU/70 kg." The specification further teaches at page 11, lines 24-27 that a neurotoxin "can be injected urethroscopically into the prostate with 200 IU with single or serial dosing. Preferably the neurotoxin is injected every three days until a therapeutic effect is achieved or up to about 2500 units." Additionally, Example 3 describes the treatment of a patient with prostate cancer with one 200 IU injection of botulinum toxin into the external urethral sphincter and the resulting relief from the prostate cancer symptom of pain. Based on

this disclosure, Applicant submits that the recitation "a therapeutic amount of a botulinum toxin" is clear.

The Examiner is respectfully requested to reconsider the rejection under 35 U.S.C. § 112, second paragraph.

The Rejection of Claims 1-19 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-19 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). With this standard in mind, the rejections raised by the Examiner are discussed below.

The claims are directed to a method of alleviating a symptom of prostate cancer, the method comprising the step of administering a therapeutic amount of a botulinum toxin into the prostate gland or a portion of the lower urinary tract of a patient with prostate cancer, thereby alleviating a symptom of prostate cancer.

Specifically, the rejection states that "the breadth of the claims is directed to prostate cancer treatment . . . ." The rejection also states that "treatment or cure of prostate cancer" with botulinum toxin is unpredictable. The rejection also states that "the specification does not provide examples of treating prostate cancer or curing prostate cancer." The reasoning with regard to the lack of enablement rejection is based on these presumptions. Applicant disagrees with this reasoning, because, as noted above, the pending claims are not directed to treatment or

cure of prostate cancer. Applicant submits that the pending claims are fully enabled over the entire scope of alleviating symptoms of prostate cancer in patients with prostate cancer.

The specification teaches, at page 9, lines 22-24, that "[s]ymptoms of prostate cancer and conditions associated with prostate cancer may include pain." Applicant notes that it has been determined by the courts, that no working examples are required to enable a patent application. *In re Borkowski et al.*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). The specification, here, however, contains at least one working example, Example 3, acknowledged in the rejection to disclose treatment of a patient having prostate cancer with botulinum toxin, and the resulting relief from the symptom of pain. Thus, the specification discloses a correlation between treatment of prostate cancer with botulinum toxin and alleviating a symptom of prostate cancer (pain). Applicant submits that this correlation is sufficient to enable the claims. While the rejection states that this example does not support the claims over the whole breadth, this reasoning is based on an interpretation of claims that includes treating or curing prostate cancer, which is not correct. When the claims are properly interpreted as covering the alleviation of the symptoms of prostate cancer, the example is fully sufficient to enable the claims.

The rejection further states that "the expectation that pain would be relieved for any and all prostate cancer patients as claimed would be unreasonable" due to "the age of the patient, complexity of his condition and treatments." Applicant disagrees with this analysis for two reasons. First, it is well settled that the Examiner can not rely on general conclusions of "basic knowledge" or "common sense." Rather, evidence is required. *In re Lee*, 277 F.3d 1338, 1345-46 (Fed. Cir. 2002). In the present case, no evidence has been presented to support the assertions that the patient's age, complexity of his condition and treatments would have any effect on the efficacy of botulinum toxin with regard to relief of pain associated with prostate cancer.

Second, Applicant is not required to show efficacy of the treatment to the degree noted in the rejection. As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). This is true, even when the evidence is in the form of *in vitro* or *in vivo* animal model example; in the present case, however, a human example is shown. Applicant submits,

therefore, that Example 3 provides a reasonable correlation between the use of botulinum toxin and alleviating a symptom of prostate cancer.

Regarding Examples 7-9, which the rejection has characterized as prophetic examples, the rejection reasons that "one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention" in part, because the results of Examples 7-9 are not shown and because "botulinum toxin primarily affects neurological dysfunction but not prostate cancer." As noted above, the claims are not directed to treating prostate cancer; therefore this reasoning is not appropriate in analyzing claims directed to the treatment of prostate cancer.

Furthemore, Examples 7-9 describe protocols to be undertaken in studies or trials with human patients. In the situation where human clinical trials have been initiated for a therapeutic product or process, it should be presumed that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility. See MPEP § 2107.03 (emphasis in original). Thus, Examples 7-9 further support the conclusion of a reasonable correlation of therapeutic use; that a correlation of the use of botulinum toxin for the alleviation of symptoms of prostate cancer.

The rejection further states that "the state of the art teaches that large controlled trials are absolutely required to establish the role of botulinum-A toxin injections in the fields of urology and neuroulology on evidence based medicine," in support of the finding of nonenablement. Applicant submits that this standard is in inappropriate, as is confuses the standards for patentability with the requirements of FDA approval. FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) (citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994)), nor is an applicant required to demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. MPEP § 2107.01 and cases cited therein. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. It is improper to request evidence regarding the degree of effectiveness. MPEP § 2107.03 and cases cited therein (emphasis in original.) Applicant submits, therefore, that the

fact that further testing will be needed to meet the requirements for drug approval has no bearing on the enablement analysis.

Finally, the rejection states that the effects and doses of various types of botulinum toxin in the method are not disclosed in the specification, and that one cannot correlate generic therapeutic amount of botulinum toxin B, C, D, E, F and G as claimed. Applicant submits again that this standard, requiring a rigorous or an invariable exact correlation, and requiring evidence of the degree of effectiveness, is inappropriate. Instead, a reasonable correlation is all that is required. U.S. Patent No. 5,837,265 (of record) teaches that various types of botulinum toxin (classified into seven serotypes, A through G, on the basis of the immunological properties) have similar structure and pharmacological actions (see U.S. Patent No. 5,837,265, col. 1, lines 56-60). It is known that all of the botulinum toxins types A-G cleave cellular protein substrates which are involved in the release of the acetylcholine neurotransmitter into the synaptic cleft of neurons in the peripheral cholingergic nervous system. Applicant submits, therefore, that the pharmacological similarity of botulinum toxin B, C, D, E, F and G to botulinum toxin A provides a reasonable correlation of the toxins' pharmacological activity. Applicant notes that this information was provided in response to the previous Office action; however, the current rejection does not address this information.

The rejection discusses the evidence regarding enablement that was presented in the previous Office action response. Regarding Michl and Gress, *Curr Cancer Drug Targets* 2004 4:689-702, the rejection states that the reference teaches bacterial toxins, but not botulium toxin, and teaches solid tumors, but not prostate cancer. The rejection concludes that the reference is not relevant. As noted in the prior response, however, Michl and Gress establish a general correlation between the use of toxins and the treatment of cancers. Applicant has provided evidence that botulinum toxin can be used to treat a symptom of prostate cancer, in particular by providing a working example showing the alleviation of at least one symptom in a patient with prostate cancer.

Regarding the Geurcini, et al., references (Geurcini, et al., *Eur. Urol. Suppl.* 2005 4:150 and Geurcini, et al., *European Association of Urology* (EAU) 20th Congress, March 16-19 (2005), Istanbul, Turkey), the rejection states that the single patient with an adenocarcinoma (e.g., a prostate cancer) was not considered for PSA evaluation, and this patient was not expected to demonstrate improvement in PSA level. The rejection concludes that "the reference appears

to acknowledge that prostate cancer would not be treated and/or improved as a result of administration of botulinum toxin to a patient with prostate cancer." Applicant disagrees with this interpretation of the references. The references do not teach or suggest that the adenocarcinoma patient was not expected to demonstrate improvement in PSA level or that the patient could not be treated with botulinum toxin. Rather, the omission of the adenocarcinoma patient from the PSA evaluation was likely due to the fact that the results would have skewed the PSA results in the BPH patients. In fact, these references show improvement of symptoms in patients with BPH and adenocarcinoma after intraprostatic injection of botulinum toxin. The demonstrated improvements include reduction of prostate weight and decrease of urinary retention, for example. These are some of the symptoms that can arise from prostate cancer, as discussed in the specification (see Background). Therefore, these references that teach that botulinum toxin could be used effectively in the treatment of symptoms of prostate cancer. Indeed, these authors conclude (see Conclusions) that botulinum toxin is an "alternative to surgery in high grade voiding dysfunction, for BPH *or cancer*, particularly in patients at risk" (emphasis added).

In summary, Applicant has provided a specification which describes the alleviation of symptoms of prostate cancer with botulinum toxin through a detailed description of the invention and working examples. The description provides a reasonable correlation between the disclosed methods and the claimed subject matter. The application of safety and efficacy standards for pharmaceutical-type inventions is not required, and is contrary to established case law. Applicant therefore submits that the pending claims are fully enabled and respectfully requests reconsideration.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. Applicant attempted on several occasions to schedule a telephonic interview with the Examiner to discuss the final rejection; however, no interview was scheduled. Should there be any outstanding issues in this application, the Examiner is invited to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-1970, if not otherwise specifically requested. The

undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-1970.

Respectfully submitted,

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